Gynecol Surg (2010) 7:19–21
DOI 10.1007/s10397-008-0457-z

COMMUNICATION

Metastatic breast ductal carcinoma detected in a toremifene-associated endometrial polyp: case report and literature review

Marta Rodrigues · Sandra Batista · Graça Ramalho · Enrique Dias

Received: 24 October 2008 / Accepted: 16 December 2008 / Published online: 10 February 2009

Abstract Uterine metastases are rare events, but when they occur, the first extragenital neoplasm responsible is breast carcinoma. Toremifene, used in breast cancer hormonotherapy, has a partial estrogenic agonist effect in the endometrium, responsible for potential abnormalities, like polyps. A 53-year-old woman, receiving toremifene due to previously excised breast ductal carcinoma, presented with endometrial thickness during an abdominopelvic ultrasound follow-up. Hysteroscopy revealed an endometrial polyp, which was removed. Microscopic examination showed infiltration by a malignant ductal pattern neoplasm, with signet ring cells. The patient underwent hysterectomy and bilateral salpingo-oophorectomy. The final pathological diagnosis was metastatic breast carcinoma to the endometrium and cervix. This is the first reported case of breast metastases detected in a toremifene-associated endometrial polyp.

Keywords Endometrial polyp · Uterine metastases · Breast cancer · Toremifene therapy

Introduction

The female reproductive tract, especially the ovaries and vagina, are at risk of metastatic involvement from extragenital neoplasm [1]. The uterus is seldom involved, and when it occurs, the first extragenital neoplasm responsible is breast cancer (in 42.9% of cases). Metastization is mainly to the myometrium and, exceptionally, to the endometrium [2].

Metastization to an endometrial polyp is an even rarer occurrence. To our knowledge, there are only 11 cases in the literature of endometrial polyp involvement by a metastatic neoplasia: one case of cutaneous melanoma [3] and breast cancer in the others [4–12]. Of these latter, seven patients were reported to be receiving adjuvant endocrine treatment with tamoxifene at the time of the diagnosis [6, 8–12].

We report a case of metastatic disease from breast ductal carcinoma, detected in an endometrial polyp, in a patient receiving toremifene as adjuvant endocrine treatment, found also to have involvement of the endometrium and cervix.

Case report

In 2003, a 53-year-old gravida 2 para 2 caucasian female underwent a right modified radical mastectomy with ipsilateral axillary lymphadenectomy (Madden technique), due to a 35×40 mm multifocal infiltrating ductal breast carcinoma of the right upper outer quadrant. Sixteen of 18 axillary lymph nodes resected showed evidence of metastatic involvement. Both estrogen and progesterone receptors were positive and Cerb-B2 oncogene was negative. The tumor was reported as $pT_2N_{3a}M_x$ (according to the 2002 American Joint Committee on Cancer staging system for breast cancer). Postsurgery treatment consisted of six-cycle multiagent chemotherapy (with 5-fluorouracil, adriamicine, and cyclophosphamide), external beam radiotherapy (50 Gys), and toremifene (60 mg/day).

M. Rodrigues (✉) · S. Batista · G. Ramalho
Department of Obstetrics and Gynecology,
Vila Nova de Gaia/Espinho E.P.E. Hospital Center,
Avenida João Paulo II, 479, 4410-406 Arcozelo,
Vila Nova de Gaia, Portugal
e-mail: martaacrodrigues@gmail.com

E. Dias
Department of Oncology,
Vila Nova de Gaia/Espinho E.P.E. Hospital Center,
Vila Nova de Gaia, Portugal

Follow-up was uneventful for 3 years. After that period, a routine abdominopelvic ultrasound showed an endometrial thickening of 13 mm. The patient was asymptomatic and the gynaecological examination was normal. A transvaginal ultrasound with hysterosonography revealed the presence of a cystic intracavitary polypoid mass, measuring 24.9×20.1 mm, originating from the anterior uterine wall. Adnexes had a normal appearance. Surgical hysteroscopy was performed, confirming the presence of a large, nacreous, hypervascular polypoid mass, originating from the anterior and left lateral uterine walls, which was removed with bipolar spring electrode. The microscopic examination showed fragments of endometrium, some with polypoid morphology with simple glandular hyperplasia. In one fragment, the fibrovascular stroma was infiltrated by malignant neoplasm of ductal pattern and some signet ring cells.

The patient underwent a positron emission tomography with 2-deoxy-2-[^{18}F]-fluoro-D-glucose, which revealed an intense uptake in the uterine area and excluded the presence of metastatic disease in other sites. Total abdominal hysterectomy and bilateral salpingo-ophorectomy was then performed. On exploration, the uterus appeared enlarged, the adnexes were normal, and no gross evidence of tumor was observed elsewhere in the abdominal cavity.

Macroscopic examination of the specimen showed an enlarged uterus with unremarkable serosal surface, but with slight cervical irregularity and thickened endometrium. Both fallopian tubes and ovaries were grossly normal. Microscopically, the endometrium was diffusely infiltrated by a malignant epithelial neoplasm, consisting mainly of isolated cells with intracitoplasmatic vacuoles and some poorly differentiated residual glands. The tumor also invaded the cervix. The myometrium, ovaries, and fallopian tubes were free of tumoral infiltration. Washing cytology was negative for the malignant cells. The final pathological diagnosis was metastatic breast ductal carcinoma to the endometrium, endocervix, and exocervix.

After surgery, the patient underwent a cycle of palliative external beam radiotherapy (50 Gys) and began anastrazol (1 mg/day) in replacement of toremifene. She remained clinically well and follow-up exams did not show any sign of relapse for 15 months when she was admitted to the hospital due to syncope and right hemiparesis. Brain computerized axial tomography was inconclusive, but brain nuclear magnetic resonance revealed metastatic foci in the third ventricle, right orbit, and right temporal fossa and several lytic lesions on the scull. Bone isotopic scan detected extensive bone metastization (scull, humeri, scapulae, sternum, ribs, vertebral bodies, hip bones, and femurs). It was decided to initiate cerebral palliative radiotherapy but the patient died 1 week later.

Comments

Isolated uterine metastases, without ovarian involvement, are very unusual and are presumably from hematogenous origin [2]. The extragenital neoplasm most often metastasizing to the uterine cervix or corpus are the breast (47.3%), stomach (29%), cutaneous melanoma (5.4%), lung (4.3%), colon (3.2%), pancreas (3.2%), and kidney (3.2%) [2, 3], probably reflecting their prevalence in the adult female population [5].

Endometrial metastases in the absence of myometrial involvement are uncommon. Kumar and Hart [3] found only two cases of endometrial secondary among 52 metastatic uterine corpus neoplasms. Metastases to an endometrial polyp are even rarer, with only 11 cases described in the literature [4–12].

Toremifene, a chlorinated derivative of tamoxifen, developed in the 1980s to improve its risk–benefit profile, is a selective estrogen receptor modulator and is widely used as adjuvant treatment of advanced, endocrine-responsive breast carcinoma due to its antiestrogenic effect in the breast. In the endometrium, similarly to tamoxifen, it has a partial estrogen receptor agonist effect, responsible for endometrial abnormalities, as simple and complex hyperplasia, with and without atypia, polyps [13, 14, 16], and carcinoma, although the incidence of the latter is lower with toremifene [14, 15]. The estrogenic effects may be local: they may be present only in a polyp but not in the surrounding endometrium [13].

Breast cancer spreads by contiguity, lymphatic channels, and blood-born metastases. The most common disseminated sites are the lungs, bones, and liver. Other common sites include the skin and brain, whereas uterine involvement is rare [16]. There are 10 cases described in the literature of breast carcinoma metastases to polyps, seven of them were related to tamoxifen [6, 8–12], but none were related to toremifene. The tumor was lobular carcinoma in five cases [7, 9–10, 12], ductal in four [4–6, 11], and apocrine in one [8]. Lobular carcinoma is the most common histological type of breast carcinoma metastasizing to the uterus. Presentation was vaginal bleeding in seven cases [4, 6, 8–10, 12], uterine enlargement in two [5, 7], and endometrial thickness in one [11]. The patients' ages ranged from 53 to 92 years (mean, 68 years). Of the five cases submitted to surgery [5–8, 11], there was endometrial involvement in one case [7] and bilateral ovarian involvement in one other [6]. Our case presented with endometrial thickness but the endometrium and cervix were also involved by the malignancy. Like in other cases [9–12], signet ring cells were present in the metastatic carcinoma. Signet ring cells may occur in breast cancers as pure cell type [16] or in conjunction with invasive lobular carcinoma or less commonly with colloid or

ductal carcinoma, and in some cases, they may be prominent in metastatic sites [11].

Uterine metastization is usually a manifestation of widespread dissemination, and patient survival is reported to be poor [1]. The interval between primary disease and uterine metastases is several months to years [1, 2]. In our patient, the disease-free period was 3 years and the uterus was the unique site of tumor spread, as in some other cases [5, 7–8, 11, 16]. The therapeutic option was surgery, although its role on disease-specific survival remains unclear. We found only one case of a patient with polyp metastases, with follow-up information after surgery, who was well after 11 months [11]. Our patient died 16 months after surgery with widespread disease. The spread of disease first to the uterus, then to bones and brain, was unusual, but it had been reported previously [16] and it may represent microscopic metastatic disease not detected during follow-up or disseminated residual pelvic disease.

We believe that this is the first reported case of breast metastases detected in a toremifene-associated endometrial polyp. Marttunen et al. [17] described one case of breast metastases in a patient receiving toremifene, at 12 months of follow-up, but they were located on both ovaries. In conclusion, it is important to bear in mind that, in patients with a history of breast carcinoma, under or with previous toremifene treatment, who present with abnormal vaginal bleeding or endometrial thickness, a metastatic involvement should be excluded.

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Mazur MT, Hsueh S, Gersell DJ (1984) Metastases to the female genital tract: analysis of 325 cases. Cancer 53:1978–1984
2. Takeda M, Diamond M, De Marco M, Quinn DM (1978) Cytologic diagnosis of malignant melanoma metastatic to the endometrium. Acta Cytol 22:503–506
3. Kumar NB, Hart WR (1982) Metastases to the uterine corpus from extragenital cancers. A clinicopathologic study of 63 cases. Cancer 50:2163–2169
4. Kumar A, Schneider V (1983) Metastases to the uterus from extrapelvic primary tumors. Int J Gynecol Pathol 2:134–140
5. Sullivan LG, Sullivan JL, Fairey WF (1990) Breast carcinoma metastatic to endometrial polyp. Gynecol Oncol 39:96–98
6. Corley D, Rowe J, Curtis MT, Hogan WM, Noumoff JS, Livolsi VA (1992) Postmenopausal bleeding from unusual endometrial polyps in women on chronic tamoxifen therapy. Obstet Gynecol 79:111–116
7. Aranda FI, Laforga JB, Martinez MA (1993) Metastasis from breast lobular carcinoma to an endometrial polyp. Report of a case with immunohistochemical study. Acta Obstet Gynecol Scand 72:585–587
8. Lambot M-A, Eddafali B, Simon P, Fayt I, Nöel J-C (2001) Metastasis from apocrine carcinoma of the breast to an endometrial polyp. Virchows Arch 438:517–518
9. Álvarez C, Ortiz-Rey JA, Estévez F, de la Fuente A (2003) Metastatic lobular breast carcinoma to an endometrial polyp diagnosed by hyteroscopic biopsy. Obstet Gynecol 102:1149–1151
10. Houghton JP, Ioffe OB, Silverberg SG, McGrady B, McCluggage WG (2003) Metastatic breast lobular carcinoma involving tamoxifen-associated endometrial polyps: report of two cases and review of tamoxifen-associated polypoid uterine lesions. Mod Pathol 16:395–398
11. Acikalin MF, Öner Ü, Tekin B, Yavuz E, Cengiz O (2005) Metastasis from breast carcinoma to a tamoxifen-related endometrial polyp. Gynecol Oncol 97:946–948
12. Al-Brahim N, Elavathil LJ (2005) Metastatic breast lobular carcinoma to tamoxifen-associated endometrial polyp: case report and literature review. Ann Diagn Pathol 9:166–168
13. Tomás E, Kauppila A, Blanco G, Apaja-Sarkkinen M, Laatikainen T (1995) Comparison between the effects of tamoxifen and toremifene on the uterus in postmenopausal breast cancer patients. Gynecol Oncol 59:261–266
14. Holli K, Valavaara R, Blanco G, Kataja V, Hietanen P, Flander M, Pukkala E, Joensuu H (2000) Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer. Finnish Breast Cancer Group. J Clin Oncol 18:3487–3494
15. Harvey HA, Kimura M, Haiba A (2006) Toremifene: an evaluation of its safety profile. Breast 15:142–157
16. Kennebeck CH, Alagoz T (1998) Signet ring breast carcinoma metastases limited to the endometrium and cervix. Ginecol Oncol 71:461–464
17. Marttunen MB, Cacciatore B, Hietanen P, Pyrhönen S, Tiitinen A, Wahlström T, Ylikorkala O (2001) Prospective study on gynaecological effects of two antioestrogens tamoxifen and toremifen in postmenopausal women. Br J Cancer 84:897–902